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ADVANCES AND HIGHLIGHTS IN PRIMARY IMMUNODEFICIENCIES 2017

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Abstract

This manuscript reviews selected topics in primary immunodeficiency diseases (PIDD) published in 2017. These include:

1. The role of follicular T cells in the differentiation of B cells and development of optimal antibody responses.

2. Impaired NFkB1 signaling in the pathogenesis of common variable immunodeficiency (CVID) revealing an association between impaired B cell maturation and development of inflammatory conditions.

3. Autoimmune and inflammatory manifestations in PIDDs in T and B cell deficiencies, as well as in neutrophil disorders.

4. Newly described gene defects causing PIDD including: *exostosin-like 3 (EXTL3), TNFα–induced protein 3 (TNFAIP3, A20), ARPC1B (actin-related protein 2/3 complexsubunit 1B), v-Rel avian reticuloendotheliosis viral oncogene homolog A (RELA), hypoxia upregulated 1 (HYOU1), BTB Domain And CNC Homolog 2 (BACH2), CD70* and *CD55.*

5. The use of rapamycin and a PI3K inhibitor, leniolisib, to reduce autoimmunity and regulate B cell function in the activated phosphoinositide 3-kinase δ syndrome (APDS).

*6.*Improved outcomes in hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) in the last decade with an overall two-year survival of 90%, in part due to early diagnosis by the implementation of universal newborn screening.

7. The demonstration of efficacy of lentiviral vector mediated gene therapy for ADA-SCID.

8. The promise of gene editing for PIDD using CRISPR/Cas9 and Zinc Finger Nuclease technology for SCID and chronic granulomatous disease (CGD).

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9. The efficacy of thymus transplantation in Europe, although associated with an unexpected high incidence of autoimmunity.

Thus, remarkable progress in the understanding and management of PIDDs reflects the current interest in this area and continues to improve the care of immunodeficient patients.

Keywords

Immunology; *primary immunodeficiency*; *NFkB*; *autoimmunity*; *IVIG*; *CVID*; *SCID*; *newborn screening*; *gene therapy*

This Advances focuses on the progress in the field of primary immunodeficiency diseases (PIDD) published in 2017. In addition to reporting new gene defects associated with PIDDs characterized by an increased susceptibility to infections, other recently described PIDDs have been found to present with significant autoimmune and inflammatory manifestations, oftentimes of more concern than the increased risk of infections.

Follicular T helper cells (T_{FH})

Follicular T helper cells (T_{FH}) have a prominent role in B cell terminal differentiation to memory B cells and plasma cells that take place in germinal centers (GC), and subsequent development of antigen specific antibody responses. **(Figure 1)** IL-12 and IL-21 stimulation induces the differentiation of T_{FH} cells, which are identified by the expression of chemokine CXC motif receptor 5 (CXCR5), chemokine CXC motif ligand 13 (CXCL13), inducible T-cell costimulator (ICOS), programmed cell death 1 (PD-1), B-cell lymphoma 6 (BCL6), B- and T-lymphocyte attenuator (BTLA), and SLAM-associated protein (SAP). Increased numbers of peripheral T_{FH}like cells have been described in autoimmune disorders, including psoriasis, lupus erythematosus and rheumatoid arthritis. Conversely, impaired differentiation of T_{FH} cells has been reported in PIDDs, such as ICOS deficiency, and the immunodeficiencies caused by STAT1 gain of function (GOF) and STAT3 loss of function (LOF). Current research efforts are aimed at further characterizing the induction and regulation of these cells. Hosokawa et al.[1] reported IL-21 protein expression by IκBNS binding to the *IL-21* gene promoter site in CD4 T cells. Previous data suggested that overexpression of *achaete-scute homologue 2 (ASCL2)* induces T cell differentiation into T_{FH} cells.[2] Interestingly, it has been shown that *IκBNS*-null T cells overexpressing *ASCL2* do not develop into T_{FH} cells, while overexpression of both *IκBNS* and *ASCL2* rescues the phenotype. These data indicate that IκBNS might act downstream of the ASCL2 transcription signal pathway. T_{FH} cell differentiation induced by coculture with thymic stromal lymphopoietin (TSLP)-activated dendritic cells (DCs) was reported by Pattarini et al.[3] They further characterized OX40-ligand as the most essential cell to cell ligand for this process and found that the resulting antibody class secretion was predominantly IgE, suggesting that this interaction results in T_H2 bias. Achour et al.[4] reported the negative influence of B regulatory cells (Breg) on T_{FH} differentiation induced by IL-12 and IL-21 *in vitro*, with decreasing both expression of surface markers as well as their capacity to induce B cell differentiation and antibody production. Presence of Bregs was associated with an expansion of follicular regulatory T cells, which were characterized by the simultaneous

expression of PD-1, CXCR5 and FOXP3. Because of the importance of ICOS-ICOSL binding to mediate B cell differentiation and antibody production by T_{FH} cells, Lownik et al.[5] asked whether proteases involved in the shedding of ICOSL from B cells could affect antibody production. They found that a disintegrin and metalloprotease 10 (ADAM10), but not ADAM17, was the most significant enzyme that participated in the cleavage of ICOSL and therefore in the activation of B cell differentiation in GC. By using mouse models, both ADAM10 and ADAM17 were shown to cleave ICOSL, however, most of the effect could be attributed to ADAM10 alone. Given the role of T_{FH} cells in autoimmune conditions and in antibody deficiencies **(TABLE 1)**, the elucidation of these molecular mechanisms, including the cytokines involved, could lead to the development of strategies helpful in the diagnosis and management of disorders of antibody production.

NFkB1 in CVID

Deleterious monoallelic mutations in *nuclear factor κB subunit (NFκB)1* (p105/p50) have been demonstrated in patients with CVID and reported to be the most common genetic defect in a large cohort of 390 CVID patients, accounting for 16 (4%) cases.[6] Patients with these mutations present with reduced NFκB1 protein levels, and an expanded $CD21^{low}$ B cell subset compared with healthy controls. Clinical presentation was variable, with autosomal dominant inheritance and variable penetrance. A penetrance of 60% in a cohort of 18 individuals carrying familial *NFκB1* mutations. In a study conducted in 3 families in Finland,[7] 12 of 15 individuals carrying *NFκB1* mutations (H67R, R157X, and I553M) had developed disease, resulting in a penetrance of 80%, clinical variability and a strong environmental and/or polygenic influence in the clinical presentation of CVID. In addition to defective antibody responses, affected patients in these families presented with inflammatory bowel disease, Behcet disease, and vasculitis. **(Figure 2, TABLE 2)** Keller at al.[8] reported that B cells from some CVID patients have impaired NFκB1 signaling and calcium mobilization after B cell receptor (BCR) stimulation. This impairment was most significant in those patients with an expanded $CD21^{low}$ $CD38^{low}$ B cell subset and was associated with reduced IκBa degradation. These patients had increased frequency of autoimmunity. Of note, $CD21^{low}$ $CD38^{low}$ B cell expansion has been described in HIV infection and autoimmune conditions such as lupus erythematous. $CD21^{low}$ $CD38^{low}$ B cells from lupus patients also show reduced IκBa degradation, suggesting that this is characteristic of the cell type. Lougaris et al.[9] reported two CVID patients with monoallelic *NFkB1* mutations (A506Vfs and D191L) leading to a truncated p50 protein and absent p105, expansion of $CD21^{low}$ $CD38^{low}$ B cell, and autoimmune enteropathy. Taken together, these data contribute to the characterization of the subset of CVID patients who develop inflammatory and autoimmune complications, who are likely to present with an expansion of $CD21^{low}$ $CD38^{low}$ B cells and might have monoallelic mutations in *NFκB1.*

Immune consequences of splenectomy and neonatal thymectomy (TABLE 3)

Patients who have been splenectomized are considered to be at significant risk of severe bacterial infections, even after pneumococcal immunization. Karasatova et al.[10] investigated

the antipneumococcal-specific lymphoproliferation in patients who have been splenectomized after spleen trauma to determine whether T cell function was impaired. After pneumococcal immunization, there was a decrease in antigen specific lymphoproliferation, which was most significant for the T_H1 cell subset, suggesting that the spleen is important for optimizing both T and B cell responses. Asplenic children with heterotaxy syndrome similarly have a significantly increased risk of invasive bacterial infections, as compared with heterotaxy syndrome patients with a normal spleen or polysplenia (50% vs 8% respectively). However, when parameters of B cell immunity were investigated, there were no significant differences between these two groups with respect to switched memory B cells, immunoglobulin levels and antigen-specific antibody responses.[11]

The clinical consequences of neonatal thymectomy continue to be investigated. It is uncertain whether the mild to moderate T cell lymphopenia that follows complete thymectomy in some infants undergoing heart surgery is a risk factor for autoimmunity and for increased susceptibility to infections.[12] Silva et al.[13] studied seven young adults who were thymectomized in infancy and did not find clinical manifestations of autoimmunity or increased allergic disease; however, they presented with positive autoantibody profiles which might confer future risk of disease. Gudmundsdottir et al.[14] studied the clonality of T and B cell repertoires in 11 individuals 18 years after thymectomy. Compared to healthy controls, CD4 T cell and CD8 T cells had higher measures of clonality in thymectomized individuals, and the degree of clonality was inversely correlated with the number of naïve T cells. B cell repertoire was not affected. Possible explanations include the relative preservation of regulatory T cells and limited follow up. Both the degree of clonality and presence of autoantibodies might be predictors of future autoimmune conditions and be best characterized with prolonged follow up.

Autoimmunity and inflammation in Primary Immunodeficiencies (TABLE 4)

Familial Mediterranean Fever (FMF) is caused by a genetic defect in the *familial mediterranean gene (MEFV)* resulting in a deficiency of pyrin, a protein that plays a role in inflammation and infections. FMF is characterized by inflammation episodes triggered by emotional or physical stress. Using transcriptome analysis in neutrophils sampled from FMF patients during attacks and in remission, Skendros et al.[15] focused on the overexpression of the protein regulated in development and DNA damage responses 1 (REDD1). During autophagy, an intracellular vesicle develops to enclose cytoplasmic components and fuses with lysosomes to form the autolysosome, where contents are degraded. Autolysosomes that are induced by REDD1 activation contain pyrin and NLRP3 inflammasome. Inflammasomes are multiprotein complexes that assemble in macrophages after different stimuli, such as bacterial products. These complexes activate the expression and secretion of inflammatory mediators. A mutated pyrin impairs autolysosome formation, resulting in increased IL-1β secretion and neutrophil extracellular traps (NET) release. REDD1 is expressed in response to epinephrine stimulation, usually during stress conditions, which might explain the association of stress and inflammation episodes in FMF patients.

A proteomics study in a THP-1 macrophage cell line and in primary monocyte-derived macrophages stimulated with lipopolysaccharide (LPS) showed that Bruton’s tyrosine

kinase (BTK), a signal transducer essential for B cell development, also regulates the activation of the NLRP3 inflammasome.[16] Testing cells from patients with X-linked agammaglobulinemia or cells from healthy controls exposed to ibrutinib, a BTK inhibitor, resulted in reduced IL-1 secretion and inhibition of the inflammasome. Ito et al.[17] reported that BTK inhibitors reduced IL-1 secretion in LPS-primed mouse peritoneal macrophages, and also in macrophages stimulated by other NLRP3 inflammasome activators, but not when stimulated by polydA:dT, an activator of the AIM2 inflammasome. BTK is therefore necessary for the activation of the NLRPR3 inflammasome, and BTK inhibitors currently used in the treatment of B cell lymphomas are now proposed for use in the management of NLRP3-mediated autoimmune and inflammatory conditions. The role of DNA demethylation in the activation of the inflammasome was explored by Vento-Torno et al.[18] LPS-stimulation was shown to be associated with demethylation of inflammasome genes, *IL1B, IL1A, NLRC5, AIM2, and CASP1*. By inhibiting tet oncogene family, member 2 (TET2), a regulator of gene demethylation, secretion of IL-1β was downregulated, providing a novel pathway to inhibit mechanisms of inflammation.

Widdrington et al.[19] reported reduced TNFα secretion by LPS-primed THP-1 macrophages due to mitochondrial DNA damage, a process often observed in sepsis. Other findings included decreased TLR4 cell surface expression and decreased interferon secretion. These changes were partially reversed when IFNγ was added to the cell cultures. The authors suggest that these mechanisms might be of significance in patients with sepsis, and there might be a role for the use of IFNγ to reverse the immunosuppression often observed during these events.

Autoimmune and inflammatory manifestations are being recognized in PIDDs as much as their characteristic susceptibility to infections. Fischer et al.[20] at the Le Centre Reference Deficits Immunitaires Hereditaires (CEREDIH) French national PIDD registry study group reported that the frequency of autoimmune disorders in 2,183 patients with PID was as high as 26%. Autoimmune cytopenia was at least 120 times more frequent than the general population. Other frequent autoimmune/inflammatory diseases include inflammatory bowel disease and arthritis. The greatest risk for these manifestations was in T cells deficiencies and in CVID. Survival was reduced in those patients presenting with autoimmunity and inflammation.

Analysis of specific PIDDs reveals distinct profiles with regards to inflammation. In the CGD French cohort, 71 of 81 CGD patients showed an inflammatory condition,[21] and 50% of these events involving the gastrointestinal tract.[22] Autoimmunity has also been reported in X-linked CGD carriers. Battersby et al.[23] identified 81 X-linked CGD female carriers in the UK CGD registry. Sixty-three (79%) subjects reported autoimmune skin conditions: photosensitivity, rashes, and eczema. Three of the carriers had inflammatory bowel disease, and 18% were diagnosed with a lupus-like disorder. Marciano et al.[24] reported on a cohort of 93 X-linked CGD carriers followed at the National Institutes of Health. Thirty-one patients (33%) reported autoimmune or inflammatory symptoms, including discoid lupus erythematosus, photosensitivity, and gastrointestinal symptoms. The difference of frequency of autoimmunity reported in both cohorts might be explained by the reporting definition of autoimmunity. While autoimmunity was not associated with oxidative burst capacity,

measured by dihydrorhodamine assay (DHR), an increased frequency of infections was observed in X-linked CGD carriers with a percentage of DHR-positive cells less than 20%. In a study of eight patients with leukocyte adhesion deficiency (LAD),[25] six had autoantibodies, three patients developed autoimmune conditions: autoimmune diabetes, autoimmune hemolytic anemia and Crohn's-like colitis and arthritis. The experience with this small cohort suggests that LAD patients are at risk for autoimmunity; a larger experience is needed to define this risk. Moutsopoulous et al.[26] reported the successful use of ustekinumab, a monoclonal antibody that inhibits IL-12 and IL-23, in a 19year-old patient with LAD and chronic severe gingival ulcers and a sacral ulcer. The researchers had previously found increased secretion of IL-17 and IL-23 in periodontal lesions from LAD patients and in animal models. Clinical improvement was observed after 3 weeks of treatment. After a year, all lesions healed, suggesting a significant role of neutrophils in the regulation of inflammation. Monoallelic mutations in the *IKAROS family zinc finger protein 1 (IKZF1)* gene have been shown to cause B cell deficiency and variable hypogammaglobulinemia.[27,28] Hoshino et al.[29] found that four of nine patients with *IKZF1* mutations had autoimmune disease: immune thrombocytopenic purpura, IgA vasculitis, and systemic lupus erythematosus. The development of autoimmune and inflammatory manifestations in PIDDs is mostly attributed to impaired mechanisms of immune tolerance, including regulatory T cells (Treg). Evidence of defective Treg activity was studied in patients with immunodeficiency due to RAG mutations.[30] RAGdeficient Treg cells demonstrated reduced repertoire and reduced capacity to suppress T cell activation, as compared with control Treg cells, suggesting a novel mechanism participating in the development of autoimmunity.

Recently reported primary immunodeficiencies

The Primary Immunodeficiency Diseases Committee of the International Union of Immunological Societies convened in February 2017 and issued update reports on the traditional and the phenotypic classification of PIDDs.[31,32] There have been recorded 354 inborn errors of immunity, and 344 genes linked to PIDDs. The term "inborn error of immunity" was introduced to include conditions that are not mainly characterized by susceptibility to infections, such as autoinflammatory conditions. The identification of genes causing PIDDs is fueled by "non-biased" molecular approaches using whole exome sequencing (WES) and copy number variant (CNV) analysis by microarray. In a cohort of 278 families with PIDDs of unknown genetic cause, this approach identified a candidate molecular etiology in 110 (40%) cases, leading to management changes in 60 cases. Eight of these cases were identified by CNV analysis. This study demonstrates the value of using these molecular approaches, at least similar to the diagnoses obtained using targeted sequencing in this scenario, with the advantage of possibly identifying causative genes not previously described. When SCID phenotype is clear, targeted gene sequencing for known genes might be considered before WES, considering that currently a minority (10–15%) of SCID cases remain without a genetic diagnosis.

Newly described gene defects causing PIDD **(Table 5)** include: *exostosin-like 3 (EXTL3), TNFα–induced protein 3 (TNFAIP3, A20), ARPC1B (actin-related protein 2/3 complex-*

subunit 1B), hypoxia upregulated 1 (HYOU1), BTB Domain And CNC Homolog 2 (BACH2), CD70 and *CD55.*

WES performed in patients with skeletal dysplasia, developmental delay and variable T cell immunodeficiency demonstrated missense mutations in *EXTL3,* a glycosyltransferase involved in heparan sulfate (HS) biosynthesis.[33,34,35] Fibroblasts from affected patients showed increased fibroblast growth factor 2 signaling and reduced IL-2 induced STAT5 phosphorylation. These defects were reversed with expression of normal EXTL3 protein. Enzymatic activity of EXTL3 was shown to be severely reduced. Thymus development in extl3-mutant zebrafish was reduced compared to controls zebrafish embryos.

TNFAIP3 (A20) downregulates the activation of the NFκB pathway by acting upstream of NFκB essential modulator (NEMO), a regulatory subunit of the IκB kinase (IKK) complex. Zhou et al.[36] reported that heterozygous LOF mutations in *TNFAIP3* (*HA20*) can cause an autoinflammatory disease. These mutations induce increased NFκB signaling and phosphorylation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinases. *TNFAIP3* (*HA20*)-associated mutations were found in six unrelated families who mostly presented with childhood-onset systemic inflammation and a 'Behçet-like' disorder. By using WES in an infant with lymphadenopathy, splenomegaly and persistent fever, Takagi et al.[37] found a biallelic mutation in the *TNFAIP3* (*HA20*) gene, predicting a truncated protein. Phosphorylation of IKK and NF-κB was increased in patient-derived T cells. Mutant *TNFAIP3* (*HA20*)–transfected cells showed increased TRAF6 polyubiquitination, suggesting the loss of TNFAIP3 (A20) deubiquitination activity. Cohort studies have further defined the spectrum of clinical manifestations of TNFAIP3 (A20) deficiency, including Behcet disease, Crohn's disease, periodic fever with aphthous pharyngitis and adenitis (PFAPA), polyarticular juvenile idiopathic arthritis, and psoriatic arthritis. [38,39]

Badran et al.[40] identified a heterozygous splicing mutation in *v-Rel avian reticuloendotheliosis viral oncogene homolog A (RELA),* encoding the NF-κB subunit RelA that segregated with autosomal dominant mucocutaneous ulcerations, dependent on anti-TNF inhibitors. Patients had reduced RelA expression and increased TNF-induced cell death in fibroblasts, but not in lymphocytes. This report supports the essential role of RelA to maintain the epithelial barriers and regulate TNF-induced cell death in chronic mucocutaneous ulcerations.

The Arp2/3 complex is essential in actin polymerization, endocytosis and cytokinesis. Two of the seven subunits are actin-related proteins of the Arp2 and Arp3 subfamilies. The other 5 regulatory subunits are ARPC1 (actin-related protein complex-1), ARPC2, ARPC3, ARPC4, and ARPC5. Three groups independently reported that *ARPC1B* mutations lead to an inflammatory syndrome with platelet developmental arrest. [41,42,43] Patients showed small volume platelets, similar to those seen in Wiskott Aldrich Syndrome. They also had vasculitis and inflammatory bowel disease. Because the isoform ARPC1B is expressed exclusively in hematopoietic cells, defects are not seen in fibroblasts or other cells lines, which express ARPC1A. A zebrafish model reproduced the findings, and wild-type ARPC1B was able to rescue platelet and T cell development.

In a patient with a history of recurrent oral herpes virus infections and recurrent hypoglycemia, Haapaniemi et al.[44] found compound heterozygous missense mutations in the *HYOU1* gene, by WES analysis. The patient had neutropenia that resolved with GCSF treatment and was receiving immunoglobulin replacement because of the use of rituximab to treat Takayasus' arteritis. Mutant HYOU1 proteins showed ectopic protein binding and altered expression of proteins involved in oxidative metabolism.

Afzali et al.[45] used WES analysis in three patients with a history of early onset autoimmune gastrointestinal disease and found heterozygous mutations in *BACH2*. All three developed a CVID picture with absent antibody responses to vaccinations. BACH2 regulates the control T cell effector lineages and promotes Tregs. BACH2 deficient mice showed absent Treg cells and an excess of memory/effector T cells, resulting in autoimmunity. Class switch recombination was also impaired. The authors concluded that BACH2 haploinsufficiency accounts for the defect of antibody response and autoimmunity.

Two groups independently reported the association of CD70 deficiency and high susceptibility to develop Epstein Barr virus-induced lymphomas.[46,47] They demonstrated reduced anti-viral T cell cytotoxicity, similar to previously observed in CD27 deficiency, underscoring the role of CD27CD70 interaction for antiviral immunity.

Homozygous deleterious mutations in *CD55* was associated with complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy (CHAPLE) syndrome in eleven patients, who were first investigated because of early-onset inflammatory bowel disease.[48] Five of the patients presented with hypogammaglobulinemia and frequent respiratory infections. CD55 is also known as complement decay accelerating factor, which helps to control damage to host cells. This study showed that absence of CD55 leads to complement hyperactivation in T cells, which could be reversed with CD55 reconstitution. Kurolap et al. [49] reported six patients from a large family presenting early in life with protein-losing enteropathy, thrombopathy and absent CD55 expression. Treatment of three of these patients with eculizumab (anti-CD5 monoclonal antibody) resulted in marked reduction of complement activation, increase in serum albumin and protein concentrations, and reduction of the number of stools.

Cartilage Hair Hypoplasia (CHH)

CHH is a skeletal disorder characterized by short limb dwarfism, sparse hair, variable immune deficiency, and a high risk of infections and neoplasia. Kostjukovits et al. [50] reported on a cohort of 56 Finnish adult and pediatric patients with CHH, carrying the g. 70A>G mutation in the *RNA component of Mitochondrial RNA processing endonuclease (RMRP)* gene. Analysis of the clinical data showed that 15 (27%) did not have symptoms of immunodeficiency, 26 (47%) had respiratory infections, and 15 (27%) had combined immunodeficiency. Only seven patients received antibiotic prophylaxis and immunoglobulin supplementation. These findings confirm previous reports of lack of correlation between clinical presentation and antibody function. The report also cautions regarding possible increased severity of clinical disease with age.

Bronchiectasis was found in 10 (29%) of 34 adult patients with CHH, associated with a history of tobacco smoking, but not with antibody defects, allergic disease or respiratory infections.[51] Deficiency of telomere homeostasis results in bone marrow failure and immunodeficiency. Because of the molecular binding of RMRP and telomerase reverse transcriptase (TERT), two studies examined whether telomere length was shortened.[52,53] Compared with matched healthy controls, median telomere length in peripheral blood cells was significantly shorter in CHH, but not in mutation carriers. Both telomere length and telomerase activity were affected in lymphocytes from CHH patients. The mechanisms for these findings are still not clearly defined and might have implications with worsening of clinical symptoms with age.

Activated phosphoinositide 3-kinase δ syndrome (APDS)

APDS is an autosomal dominant immune disorder caused by GOF mutations in *phosphatidylinositol 3-kinase, catalytic, delta (PIK3CD)*, which encodes the p110δ catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ). Affected individuals present with a persistent and dysregulated cell activation state, with impairment of both T and B cell differentiation and function. In a cohort of 53 APDS patients,[54] sinopulmonary infections (98%) and nonneoplastic lymphoproliferation (75%) were the most commonly observed conditions. Other common complications included herpesvirus infections (49%), autoinflammatory disease (34%), and lymphoma (13%). Neurodevelopmental delay was reported in 19% of the cohort, suggesting a possible role for PI3Kδ in the central nervous system. Immunologic testing did not identify markers associated with clinical severity. Most patients received immunoglobulin replacement and antibiotic prophylaxis. Fifty patients carried the previously reported *PIK3CD* E1021K allele, and three patients had the E525K allele. Dulau Florea et al.[55] described impaired B cell differentiation in the bone marrow of ten APDS patients, with B cell lymphopenia in peripheral blood and predominance of transitional B cells, which is consistent with the frequent presentation of APDS as CVID.

Different immunosuppressive therapies have been used for lymphoproliferative manifestations in APDS. Rapamycin is an attractive candidate because of the mechanisms involving mTOR pathways. A cohort study of 77 European patients with APDS caused by mutations in *PIK3CD* (APDS1) (n=51) or *PIK3R1* (APDS2) (n=22) described the clinical response to rapamycin: lymphoproliferation was significantly reduced (8 complete, 11 partial, 6 no remission), but bowel inflammation and cytopenias were not as successfully treated in most patients (3 complete, 3 partial, 9 no remission). Specific inhibition of PI3Kδ has shown clinical benefit in certain types of B-cell lymphomas, and several small molecules with this property have been developed.[56] A 12-week dose escalating open-label clinical trial of leniolisib, a novel PI3K inhibitor, was conducted in six patients with APDS.[57] Overall, patients showed a decrease of IgM and inflammatory markers, and normalization of transitional and naïve B cells. One patient stopped immunoglobulin supplementation. All patients showed reduction of lymph node size and spleen volume by 40%. There was recovery of cytopenias while neutropenia, transaminitis, and diarrhea, toxicities commonly associated with PI3K inhibitors did not occur. The experience of 11 patients with APDS who received HSCT because of severe immunodeficiency, presenting with recurrent infections and lymphadenopathy was reported.[58] Nine patients (81%) are alive with post-HSCT

follow-up of 8 months to 16 years. Two deaths occurred about 3 months post HSCT due to CMV and adenovirus pneumonias, and one patient died due to idiopathic pulmonary fibrosis.

Hematopoietic Stem Cell Transplantation for Primary Immunodeficiencies (Table IV)

The experience of HSCT for PIDD continues to improve over time, as reflected in several reports summarized here. Heimall et al.[59] representing the Primary Immune Deficiency Treatment Consortium (PIDTC) published a multicenter prospective observational study of HSCT for severe combined immunodeficiency (SCID) performed from 2010 to 2014 in the United States and Canada; 68 patients with SCID and 32 with leaky SCID were included. The 2-year survival was over 90%, with no significant differences when considering donor source selection, conditioning, or GVHD prophylaxis. The 2-year survival was 80% for those transplanted after 3.5 months of age and with an active infection. This result in infected patients older than 3.5 months represents a significant improvement over a previous PIDTC retrospective study of SCID patients transplanted from 2000 through 2009,[60] in which the survival was 67%. In the prospective study, 25 of 59 (42%) patients diagnosed early with newborn screening or family history had an active infection before HSCT, highlighting the need to improve preventive measures. At 100 days after T-cell–replete HSCT, the risk of death or the need for a second HCT by 2 years post-HSCT were associated with T cell counts < 300 cells/μL, CD8 T cell counts < 50 cells/μL, CD45RA T cells < 10%, and polyclonal Vβ families < 13 of 24 (33% vs 11%; P =.048). Consistent with these results, a review of 273 patients receiving HSCT for a variety of malignant and non-malignant diseases (12% with PIDD) indicated that a delay of CD4 T cell reconstitution was associated with reactivation of adenovirus, EBV, and HHV6 but not CMV or BK virus.[61]

Dvorak et al.[62] reviewed the frequency of neurological symptoms (developmental delay, seizures, hemiplegia, cerebral palsy, blindness) in 62 SCID patients from a single center who received HSCT and survived. They measured the neurological event free survival (NEFS) and found that it was 100% at 5 years in those patients diagnosed by family history or by newborn screening (n=31). In contrast, eight of 31 (26%) SCID patients diagnosed clinically, i.e., presenting with infections developed neurological impairment associated with pre-HCT infections with cytomegalovirus, respiratory syncytial virus, Candida, or bacterial pneumonia (NEFS = 51% at 5 years, $p<0.001$). This study indicates that outcomes in addition to overall survival are important in assessing various treatment approaches and further supports the benefit of newborn screening by preventing neurological damage in SCID patients.

De la Morena et al.[63] reported on a large international cohort of 176 X-linked hyper IgM syndrome patients from 28 centers, who were diagnosed between 1964 and 2013. 38% were treated with HSCT. No difference in overall survival was observed with regards to HSCT vs medical management across all years, however, there was a tendency to favor HSCT treatment when considering only those treated after 1993. Also, patients treated with HSCT

at an early age had improved survival. Liver disease and age at transplantation older than 10 years were negative risk factors for survival.

Miot et al.[64] gathered the worldwide experience of patients with hypomorphic NEMO mutations who received HSCT and presented a cohort of 29 patients from which 10 patients were not previously reported. The engraftment rate was 93%, with 74% survival. The small number of patients did not allow for strong conclusions, however, the data suggested that using a carrier sister or mother as donor, mycobacterial infection pretransplant and presence of inflammatory bowel disease were risk factors for poor post-transplant outcomes.

Successful HSCT has been reported for rare primary immunodefiencies. In two siblings with Myb-like, SWIRM, and MPN domains 1 (MYSM1) deficiency, Bahrami et al.[65] used a regimen based on fludarabine and treosulfan, in consideration of the increased susceptibility to genotoxic stress. Ovadia et al.[66] reported HSCT in two siblings with RelB deficiency, presenting with severe T cell deficiency and recurrent infections. They received HSCT from a match unrelated donor with myeloablative conditioning, resulting in immunoreconstitution.

Gene Therapy for PID (Table IV)

Shaw et al.[67] reported the long-term outcomes of ten patients with adenosine deaminase (ADA) deficiency who enrolled in a gene therapy trial between 2009 and 2012. All patients received ADA-corrected autologous hematopoietic stem cells after receiving conditioning with low dose busulfan and stopping enzyme replacement therapy (ERT). Nine of 10 patients remained off ERT, and had normal lymphocyte counts and proliferative responses to mitogens at the time of the report. Three of these nine patients also stopped immunoglobin supplementation. In a safety evaluation study, genomic DNA from fifteen ADA patients treated with gene therapy using gammaretroviral-based vectors was examined for integration site distribution. The two sites most frequently found were in *MDS and EVI1 complex locus (MECOM)* and in *LIM domain only 2 (LMO2)*, near gene promoters, at sites previously observed in gene therapy trials for IL2RGSCID, WAS, and CGD.[68] Vector site integration diversity correlated with T cell clonal diversity and T-cell repertoire, as measured by vector integration site sequencing and T-cell receptor βchain rearrangement sequencing. The degree of vector integration diversity correlated significantly with the exposure to busulfan preconditioning as measured by cumulative area under the curve (cAUC) and to CD34+ cell dose. The authors concluded that vector insertions in oncogenes alone do not result in neoplasias since none have been seen in the gene therapy trials for ADA-SCID to date, and it is possible that the nature of the *ADA* gene defect might have a role in the lack of development of leukemias even when γ-retroviral vectors were used.

Significant preclinical progress towards the use of gene therapy for chronic granulomatosis disease (CGD) was reported. Sweeney et al. [69] developed a phagocyte defective mouse model in non-obese diabetic $\gamma c^{-/-}$ SCID (NOD-SCID) mice for evaluating human gene therapy for Xlinked CGD using the technology using clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR associated protein 9 (Cas9) to knock out exon 1 of the murine *cytochrome b, beta subunit (Cybb)* gene. They subsequently demonstrated the

significance of retaining intron 1 sequences to allow expression of CYBB in granulocytes from induced pluripotent stem cells (iPSC) from CGD patients with mutations in exon 5 when using an endogenous promoter.[70] The targeted insertion of the normal sequence of a *CYBB* minigene (exons 2–13) into these iPSC-derived granulocytes restored gp91phox activity. When the *CYBB* minigene was inserted into *CYBB* exon 1, there was no detectable expression, although expression was obtained when inserted into exon 2. De Ravin et al.[71] reported CRISPR/Cas9 mediated repair of the *CYBB* C676T position in mobilized $CD34^+$ HSC from two patients carrying this mutation and allowed differentiation into myeloid cells *in vitro*. Efficiency of correction was 19%, measured by oxidative capacity, compared with 95% of myeloid cells derived from an HSC control. There were no off-target insertions or deletions detected by exome sequencing. Transplant of gene-repaired human X-linked CGD $CD34^+$ HSC into NOD-SCID mice resulted in the development of functional mature human myeloid and lymphoid cells for up to 20 weeks, with functional oxidative capacity of about 14% of human myeloid cells. HSCs from a second CGD patient showed a similar degree of correction. This work helps to establish the feasibility of the CRISPR-based approach for the genetic correction of CGD and possibly other blood cell diseases.

Preclinical investigations in advancing gene therapy for SCID included the development of a lentivirus vector with the human Artemis *DCLRE1C* cDNA under transcriptional regulation of its own human Artemis promoter.[72] Over-expression of Artemis with highly active promoters had resulted in toxicity to transduced cells, therefore, the use of the autologous gene promoter was expected to be better tolerated. Transduction of human Artemis deficient fibroblasts and $CD34^+$ HSC, as well as HSC from Artemis-deficient mice, achieved significant correction of radiation sensitivity and successful *in vivo* and *in vitro* differentiation of transduced Artemis-deficient HSC into T and B cells.

Parallel to the efforts for gene editing approaches for CGD, strategies based on homology directed repair (HDR) are being optimized for SCID. Schiroli et al.[73] established a humanized mouse model to test gene editing in human hematopoietic stem cells. They used an adenoassociated virus 6 or a defective lentivirus to carry donor DNA and an electroporated zinc finger nuclease (ZFN) to insert a mini *IL2RG* gene into the *IL2RG* locus, aimed at correcting the greatest number of mutations in this gene with one strategy.

Other Therapies for PIDDs

Results of a series of twelve European patients with complete DiGeorge Syndrome (cDGS) who received thymus transplants from 2009 and 2014 were reported by Davies et al.[74] T cell reconstitution occurred 5 to 6 months post-transplant. Two patients died of pre-existing viral infections, and one died from autoimmune thrombocytopenia. Autoimmune complications were seen in seven of 12 patients, including hemolytic anemia, neutropenia, thrombocytopenia and thyroiditis. These outcomes support the effectiveness of thymus transplantation for cDGS, although concerns for the development of autoimmunity are raised.

Marciano et al.[75] studied the use of granulocyte transfusions over the past three decades in a cohort of 48 CGD patients presenting with refractory infections. The treatment was

associated with resolution in 51 of 58 infectious episodes. Analysis of multiple variables including granulocyte dose, type of infection, genetic diagnosis and demographics, suggested that lack of response was associated with older age and giving this treatment late in the course of the infection.

A deeper understanding of mechanisms of disease are prompting the use of biological agents for novel applications in PID. Weinacht et al.[76] reported the use of ruxolitinib, a JAK1/2 inhibitor, to control autoimmunity cytopenias in a patient with STAT1 GOF mutation. Immunological correlates were demonstrated, including modulation of type I and II interferons, restoration of T_H1 and T_{FH} cell responses, and improvement in T_H17 differentiation. Tabellini et al.[77] reported that NK cell dysfunction in these patients were related to unresponsiveness to IL-15. VargasHernandez et al.[78] demonstrated that use of ruxolitinib restored normal expression of perforin in NK cells and improved NK cells function in patients with STAT1 GOF.

Innovative therapeutic interventions are needed for PIDD patients. Measures of quality of life indicate that current management is accompanied by suboptimal well-being. In a study of 945 CVID patients recruited by the Immune Deficiency Foundation, [79] there was significantly decreased mental and physical well-being than the general US adult population normative sample, independent of the mode of immunoglobulin replacement. Similar decreased quality of life measures was found in children with PIDD. [80]

CONCLUSIONS

New developments in the biology of T_{FH} cells help to understand their role in the regulation of B cell responses and suggest points of intervention. In parallel, studies of NFkB1 mutations showed that intrinsic pathways of B cell activation are, in part, responsible for the expansion of immature cells and might result in CVID. WES technology has contributed to the discovery of new genes that are essential to the immune response, with gene mutations being responsible not only for the high susceptibility to infections, but also the increased risk of autoimmunity and auto-inflammation. Improved outcomes of HSCT for SCID reflect awareness, as well as the implementation of universal newborn screening for T cell deficiency. Gene therapy researchers have brought new ideas to reduce genotoxicity by using CRISPR/Cas9 and other gene-editing technologies, and gene insertion using autologous promoters.

Abbreviations

CHH	cartilage hair hypoplasia
CGD	chronic granulomatous disease
CVID	combined variable immunodeficiency
HSCT	hematopoietic stem cell transplantation
ICOS	inducible T-cell costimulator

IVIG	intravenous immunoglobulins
NFkB	nuclear factor κB subunit
PIDD	primary immunodeficiency diseases
SCID	severe combined immunodeficiency
STAT	signal transduction and activator
TFH	follicular T helper cells Tregs regulatory T cells
WES	whole exome sequencing

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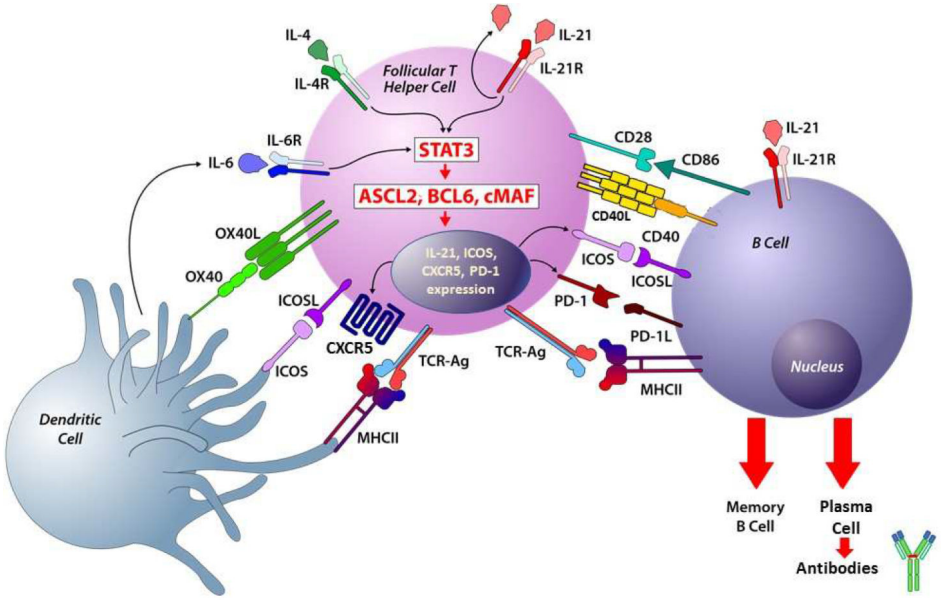

Figure 1-

Antigen presenting cells activate Follicular Helper T (TFH) cells through cell to cell interaction and IL-6. STAT3 phosphorylation in TFH results in secretion of IL-21, PD-1 and ICOS. TFH -mediated activation of B cells promote differentiation into memory B, plasma cells and antibody production.

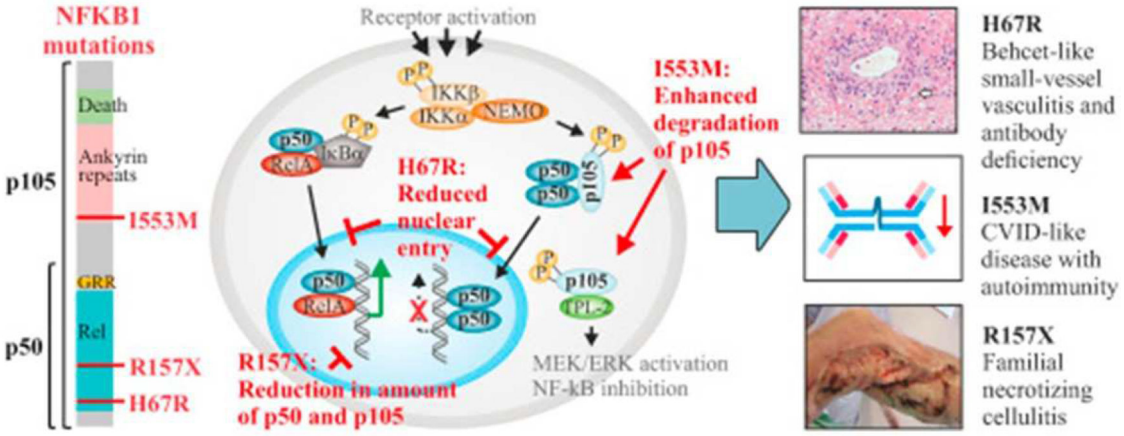

Figure 2-

NFKB1 mutations are linked to different clinical phenotypes, both autoimmunity and immunodeficiency. I533M was associated with antibody deficiency. H67R was associated with Behcet-like disease. R157X was associated with necrotizing cellulitis. Graphical Abstract from Kaustio. et al. JACI 2017 140 (3): 782–796

Table 1:

Follicular T cells (TFH) are affected in primary immunodeficiencies

Abnormality	Defective gene
Reduced frequency of TFH cells	*CD40LG, NEMO, STAT3, ICOS, BTK, IL10R, E2A*
Skewing of TFH cells to TH1 phenotype	*STAT1 GOF, STAT3*
Defective TFH cells	*SH2D1A*

From: Ma CS. Human T Follicular Helper Cells in Primary Immunodeficiency: Quality Just as Important as Quantity. J Clin Immunol. 2016;36 Suppl 1:40–7.

Table 2:

Clinical Phenotypes Associated to *NFKB1* gene mutations.

Common Variable Immunodeficiency
Inflammatory Bowel Disease
Behcet Disease
Arthritis
Familial necrotizing cellulitis
Chronic EBV infection.
EBV lymphoproliferative disease

Table 3-

Consequences of Splenectomy and Neonatal Thymectomy

Splenectomy[10,11]	Neonatal Thymectomy[12,13,14]
- Increased risk of severe bacterial infections - Decreased capacity of eliciting antipolysaccharide antibodies - Decreased anti-pneumococcal-specific lymphoproliferation.	- Decreased naïve T cells - Mild to moderate T cell lymphopenia - Increased positive autoantibody profiles without autoimmune disease. - Marked clonality in CD4 T cell and CD8 T cells

Table 4-

Autoimmunity and Inflammation in PID

- REDD1 expression in response to epinephrine stimulation might explain the association of inflammation episodes in FMF with stress.[15]
- BTK is necessary for the activation of the NLRPR3 inflammasome. A BTK inhibitor, ibrutinib, reduced IL-1 secretion and inhibited the inflammasome formation. [16]
- Inhibition of the tet oncogene family, member 2 (TET2), a regulator of gene demethylation, reduces secretion of IL-1β. [18]
- The frequency of autoimmune disorders in a French PID cohort was 26%.[20]
- 71 of 81 CGD patients showed an inflammatory condition,with 50% of events involved the gastrointestinal tract. [21]

79% of XL-CGD female carriers in the UK registry reported autoimmune skin conditions. In a cohort of X-linked CGD carriers followed at the National Institutes of Health (n=93), 31 patients (33%) reported autoimmune or inflammatory symptoms. Occurrence of autoimmunity was not associated with percentage of DHR positive cells while severe infections increased when the percentage of DHR positive cells was <20%.. [23,24]

- Use of ustekinumab, a monoclonal antibody that inhibits IL-12 and IL-23, was successfully used to treat chronic skin and mouth ulcers in a LAD1 patient. [26]
- Mutations in the *IKZF1* gene may lead to autoimmunity, in addition to B cell deficiency and variable hypogammaglobulinemia. [27]

Table 5

Recently reported PID

Gene	Inheritance	Gene Name	Phenotype
EXTL3	Autosomal Recessive	exostosin-like 3	skeletal dysplasia, developmental delay and variable T cell immunodeficiency.[34,35,36]
TNFAIP3, A20	Autosomal Dominant	TNF-α–induced protein 3	Behcet disease, Crohn's disease, PFAPA (periodic fever with aphthous pharyngitis and adenitis), polyarticular juvenile idiopathic arthritis; and psoriatic arthritis. [37,38,39]
RELA	Autosomal Recessive	Reticuloendotheliosis viral oncogene homolog A	Chronic mucocutaneous ulceration. [40]
ARPC1 B	Autosomal Recessive	actin-related protein 2/3 complex-1, subunit B.	inflammatory syndrome with platelet developmental arrest. Small volume platelets. [41,42,43]
HYOU1	Autosomal Recessive	hypoxia upregulated 1	recurrent oral herpes virus infections, hypoglycemia. [44]
BACH2	Autosomal Dominant	BTB Domain And CNC Homolog 2	common variable immunodeficiency. [45]
CD70	Autosomal Recessive	CD70	Epstein Barr virus-induced lymphomas. [46,47]
CD55	Autosomal Recessive	CD55	complement hyperactivation, angiopathic thrombosis and proteinlosing enteropathy (CHAPLE) syndrome. [48]

Table 6:

Progress in HSCT and Gene Therapy for PID

Hematopoietic Stem Cell Transplantation for PID - Two-year survival for HSCT for SCID (2010 to 2014) was reported to be over 90%.[58] - Early diagnosis (i.e. newborn screening) and management of SCID helped prevent neurologic damage. [61] - No difference in overall survival was observed with regards to HSCT vs conventional treatment in a cohort of 176 X-linked hyper IgM syndrome patients. [62] - 74% survival was reported in patients with hypomorphic NEMO mutations who received HSCT. [63] - Successful HSCT has been reported for MYSM1 deficiency and RelB deficiency. [64]
Gene Therapy for PID - Long-term follow-up of patients with ADA-deficiency underscores the improved outcomes of those who received gene therapy. [66] - Gene therapy using γ-retroviral vectors for ADA deficiency resulted in vector insertion in oncogenes, however, leukemias have not developed to date. [67] - Mouse models for gene therapy for CGD demonstrated the use of CRISPR/Cas9 technology to correct CYBB mutation in human HSC. [70] - A lentiviral vector carrying the human Artemis *DCLRE1C* cDNA under transcriptional regulation of its own human Artemis promoter was effective in correcting Artemis deficient HSC in preclinical human and mouse models. [71]